ACTA NEUROBIOLOGIAE EXPERIMENTALIS

Acta Neurobiol. Exp. 1996, 56: 359-362

Use of melatonin in circadian rhythm disorders and following phase shifts

Debra J. Skene, Stephen Deacon and **Josephine Arendt**

School of Biological Sciences, University of Surrey, Guildford, Surrey GU2 5XH, UK, email d.skene@surrey.ac.uk

Abstract. Following abrupt phase shifts (real or simulated time zone changes, night shift work) there is desynchronisation between the internal circadian rhythms (including melatonin) and the external environment with consequent disturbances in sleep, mood and performance. In humans the pineal hormone melatonin has phase-shifting and resynchronising properties with regard to a number of circadian rhythms. Suitably timed melatonin adminstration hastened adaptation to phase shift and significantly improved self-rated jet lag in large numbers of time zone travellers. Preliminary results in night shift workers showed improved daytime sleep and night-time alertness. In simulated experiments, appropriately timed melatonin improved subjective sleep, alertness and performance and facilitated the readaptation of the melatonin rhythm following a rapid 9 h advance phase shift. Melatonin has also been assessed in circadian rhythm disorders with disturbed sleep (blindness and delayed sleep phase insomnia). Compared with placebo, melatonin significantly improved sleep and synchronised the sleep wake cycle in some blind subjects. Melatonin treatment significantly advanced the sleep onset time in delayed sleep phase insomnia. Taken together these findings suggest that melatonin is of benefit in facilitating adaptation to forced phase shifts and in conditions of circadian rhythm disturbance.

Key words: melatonin, circadian rhythm disorders, phase shifts, blindness, jet lag

Review

INTRODUCTION

In all species studied to date, including man, synthesis of the pineal gland hormone melatonin has a day-night variation with peak levels occurring in the dark phase. The melatonin rhythm is an endogenous circadian rhythm which is driven by the circadian pacemaker located in the hypothalamic suprachiasmatic nuclei (SCN). In photoperiodic species the rhythmic production of melatonin conveys information about the prevailing light/dark cycle for the timing of seasonal functions.

Animal studies have demonstrated that exogenous melatonin has resynchronising properties. Melatonin injections synchronised the free running rest-activity cycles in rats kept in constant darkness (Redman et al. 1983). In addition, melatonin treatment altered the rate and direction of re-entrainment of rat locomotor activity following phase shifts (Armstrong and Redman 1985). More recently evidence has accumulated which suggests that melatonin acts *via* the SCN to affect these circadian rhythms. Melatonin receptors have been identified in the SCN of numerous species (review Morgan et al. 1994), including man (Reppert et al. 1988). The ability of appropriately timed melatonin to phase advance free running locomotor activity in rats (Redman et al. 1983) is blocked by SCN ablation (Cassone et al. 1986). *In vitro* SCN electrical activity is phase advanced by melatonin applied around the day-night transition (McArthur et al. 1991).

Whether melatonin has phase-shifting and resynchronising properties in humans, and if so, whether this will be of therapeutic benefit in facilitating adaptation to forced phase shifts and in conditions of circadian rhythm disturbances has been investigated in our laboratory. This review summarises these studies.

EFFECT OF EXOGENOUS MELATONIN

Early work showed that timed administration of melatonin to healthy volunteers (2 mg daily at 17.00 h for 4 weeks) phase advanced its own endogenous rhythm and increased self-rated evening fatigue after 4 days of treatment (Arendt et al. 1984, 1985, Wright et al. 1986). Compared with placebo, no changes in mood, cortisol, GH, LH, testosterone and T_4 levels were observed, although a small advance of the morning decline of prolactin was seen. Recently melatonin (single 5 mg dose at 17.00 h) has been shown to induce a significant suppression of core body temperature and self-rated alertness followed by a phase advance of the onset of endogenous melatonin the following evening (Deacon et al 1994). Further work has found these effects to be dose-dependent (Deacon and Arendt 1995a).

MELATONIN AND ADAPTATION TO PHASE SHIFT

Following abrupt phase shifts (real or simulated time zone changes, night shift work) there is a mismatch between the internal circadian rhythms (including melatonin) and the external environment with consequent disturbances in sleep, mood and performance. In the first placebo controlled jet lag study, melatonin (5 mg) significantly improved self-rated jet lag, daytime alertness, sleep latency and quality, and hastened the rate of resynchronisation of endogenous melatonin and cortisol rhythms (Arendt et al. 1986, 1987). A subsequent double-blind cross-over study (Skene et al. 1989) demonstrated that melatonin, appropriately timed to induce phase advances or delays, was highly effective in improving jet lag, although a small minority (10%) of subjects felt worse. Results from all placebo-controlled and uncontrolled studies (melatonin n=474, placebo n=112) indicate that, suitably timed, melatonin reduces self-rated jet lag by 50% (P <0.001) in the majority of air travellers (irrespective of age, sex and direction of travel).

The use of melatonin in field studies of shift workers is still in its infancy. A preliminary study of night shift workers showed that melatonin taken at the desired bedtime following a 8 h night shift improved self-rated sleep quality and sleep duration

with increased alertness during the work shift (Folkard et al. 1993).

Field studies are expensive and difficult to control with respect to the physical and social environment. Thus in order to address some questions about melatonin's action, simulated phase shift experiments have been set up in the laboratory. Moderately bright light (1,200 lux) at night followed by imposed darkness is used to phase shift subjects in a controlled environment. This protocol induces a gradual 9 h delay phase shift in the circadian system following which the subjects are released back into the baseline environment, simulating a rapid time zone change or a change to a new shift work schedule (Deacon and Arendt 1995b). In such simulated experiments, appropriately timed melatonin (5 mg) improved subjective sleep, alertness and performance and facilitated the readaptation of the melatonin rhythm following the rapid 9 h advance phase shift (Deacon and Arendt 1995c).

MELATONIN AND CIRCADIAN RHYTHM DISORDERS

Melatonin has also been assessed in conditions of biological rhythm disturbances with disturbed sleep (blind subjects and patients with delayed sleep phase insomnia). Compared with placebo, melatonin significantly improved sleep and synchronised the sleep wake cycle in some blind subjects (Aldhous and Arendt 1991). Intensive study of one free running blind man showed that melatonin synchronised the sleep/wake cycle (primarily by stabilising sleep onset) and reduced daytime sleepiness without synchronising the endogenous rhythms of melatonin, cortisol and core body temperature (Arendt et al. 1988, Folkard et al. 1990). Detailed investigation of the circadian rhythm abnormalities in blind subjects prior to melatonin administration is currently underway so that the timing of melatonin administration can be optimised for each individual.

An effect on sleep onset was also observed in patients with delayed sleep phase insomnia, melatonin administration (5 mg) at bedtime advancing sleep onset in all subjects (Dahlitz et al. 1991).

CONCLUSIONS

These findings suggest that melatonin is of benefit in facilitating adaptation to forced phase shifts and in conditions of circadian rhythm disturbance. Optimisation of dose and timing of administration require further investigation. Application of the human phase response curve to melatonin (Lewy et al. 1992, Zaidan et al. 1994), and knowledge of an individual's circadian status prior to melatonin administration will assist in the design of effective treatment regimens.

ACKNOWLEDGEMENTS

Clinical trials and laboratory work were supported partly by South Thames Regional Health Authority and by Stockgrand Ltd (University of Surrey, Guildford, Surrey, UK).

REFERENCES

Aldhous M.E., Arendt J. (1991) Assessment of melatonin rhythms and the sleep-wake cycle in blind subjects. In: Advances in pineal research (Eds. J. Arendt and P.Pevet). Vol. 5. John Libbey, London, p. 307-309.

Arendt J., Aldhous M., English J., Marks V., Arendt J.H., Marks M., Folkard S. (1987) Some effects of jet lag and their alleviation by melatonin. Ergonomics 30: 1379-1393.

Arendt J., Aldhous M., Marks V. (1986) Alleviation of jet-lag by melatonin:preliminary results of controlled double blind trial. Br. Med. J. 292: 1170.

Arendt J., Aldhous M., Wright J. (1988) Synchronisation of a disturbed sleep-wake cycle in a blind man by melatonin treatment. Lancet i: 772-773.

Arendt J., Bojkowski C., Folkard S., Franey C., Marks V., Minors D., Waterhouse J. (1985) Some effects of melatonin and the control of its secretion in man. In: Photoperiodism, melatonin and the pineal (Eds. D. Evered and S. Clark). Ciba Foundation Symposium 117. Pitman, London, p. 226-283.

Arendt J., Borbely A.A., Franey C., Wright J. (1984) The effects of chronic small doses of melatonin given in the late afternoon on fatigue in man:a preliminary study. Neurosci. Lett. 45: 317-321.

Armstrong S. M., Redman J. (1985) Melatonin administration:effects on rodent circadian rhythms. In: Photoperiodism, melatonin and the pineal (Eds. D. Evered and S. Clark). Ciba Foundation Symposium 117. Pitman, London, p. 188-207.

Cassone V.M., Chesworth M.J., Armstrong S.M. (1986) Entrainment of rat circadian rhythms by daily injection of melatonin depends upon the hypothalamic suprachiasmatic nuclei. Physiol. Behav. 36: 1111-1121.

Dahlitz M., Alvarez B., Vignau J., English J., Arendt J., Parkes J.D. (1991) Delayed sleep phase syndrome response to melatonin. Lancet 337: 1121-1124.

Deacon S.J., Arendt J. (1995a) Melatonin-induced temperature suppression and its acute phase-shifting effects correlate in a dose-dependent manner in humans. Brain Res. 688: 77-85

Deacon S.J., Arendt J. (1995b) Adapting to phase-shifts, I. An experimental model for jet lag and shift work. Physiol. Behav.(in press)

Deacon S.J., Arendt J. (1995c) Adapting to phase-shifts, II. Effects of melatonin and conflicting light treatment. Physiol. Behav. (in press)

Deacon S., English J., Arendt J. (1994) Acute phase-shifting effects of melatonin associated with suppression of core body temperature in humans. Neurosci. Lett. 178:32-34.

Folkard S., Arendt J., Aldhous M., Kennett H. (1990) Melatonin stabilises sleep onset time in a blind man without entrainment of cortisol or temperature rhythms. Neurosci. Lett. 113: 193-198.

Folkard S., Arendt J., Clark M. (1993) Can melatonin improve shift workers' tolerance of the night shift? Some preliminary findings. Chronobiol. Int. 10: 315-320.

Lewy A.J., Ahmed S., Latham Jackson J.M., Sack R.L. (1992) Melatonin shifts human circadian rhythms according to a phase response curve. Chronobiol. Int. 9: 380-392.

McArthur A.J., Gillette M.U., Prosser R.A. (1991) Melatonin directly resets the rat suprachiasmatic circadian clock in vitro. Brain Res. 565: 158-161.

Morgan P.J., Barrett P., Howell H.E., Helliwell R. (1994) Melatonin receptors:localization, molecular pharmacology and physiological significance. Neurochem. Int. 24:101-146.

Redman J., Armstrong S., Ng K.T. (1983) Free-running activity rhythms in the rat: entrainment by melatonin. Science 219: 1089-1091.

Reppert S.M., Weaver D.R., Rikvees S.A., Stopa E.G. (1988) Putative melatonin receptors in the human biological clock. Science 242: 78-81.

Skene D.J., Aldhous M., Arendt J. (1989) Melatonin, jet-lag and the sleep-wake cycle. In: Sleep '88. Proceedings of the Ninth European Congress on Sleep Research, Jerusalem 1988 (Ed. J. Horne). Gustav Fischer Verlag, Stuttgart, p. 39-41.

Wright J., Aldhous M., Franey C., English J., Arendt J. (1986) The effects of exogenous melatonin on endocrine function in man. Clin. Endocrinol. 24: 375-382.

Zaidan R., Geoffriau M., Brun J., Taillard J., Bureau C., Chazot G., Claustrat B. (1994) Melatonin is able to influence its secretion in humans: description of a phase response curve. Neuroendocrinology 60: 105-112.

Paper presented at the 2nd International Congress of the Polish Neuroscience Society; Session: Melatonin: origin and functions in an organism